General

Guideline Title

ACR Appropriateness Criteria® prostate cancer—pretreatment detection, surveillance, and staging.

Bibliographic Source(s)

Coakley FV, Oto A, Alexander LF, Allen BC, Davis BJ, Froemming AT, Fulgham PF, Hosseinzadeh K, Porter C, Sahni VA, Schuster DM, Showalter TN, Venkatesan AM, Verma S, Wang CL, Remer EM, Eberhardt SC, Expert Panel on Urologic Imaging. ACR Appropriateness CriteriaÂ® prostate cancerâ€"pretreatment detection, surveillance, and staging. Reston (VA): American College of Radiology (ACR); 2016. 16 p. [93 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Eberhardt SC, Carter S, Casalino DD, Merrick G, Frank SJ, Gottschalk AR, Leyendecker JR, Nguyen PL, Oto A, Porter C, Remer EM, Rosenthal SA, Expert Panels on Urologic Imaging and Radiation Oncology-Prostate. ACR Appropriateness Criteria® prostate cancer -- pretreatment detection, staging, and surveillance. [online publication]. Reston (VA): American College of Radiology (ACR); 2012. 12 p. [119 references]

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

ACR Appropriateness Criteria®

Clinical Condition: Prostate Cancer—Pretreatment Detection, Surveillance, and Staging

Variant 1: Clinically suspected prostate cancer, no prior biopsy (biopsy naïve). Detection.

Radiologic Procedure	Rating	Comments	RRL*
TRUS-guided biopsy prostate	9		O
MRI prostate without and with IV contrast	7	MRI may be performed before TRUS-guided biopsy so the targeted sample may be obtained using MRI or TRUS fusion	O

Rating Scale: 1, 2, 3 Usually not appropriate; 4, 5, 6 May be appropriate; 7, 8, 9 Usually appropriate

*Relative Radiation Level

Radiologic Procedure	Rating	Comments	RRL*
		technology in patients with appropriate targets. MRI is complementary to TRUS-guided biopsy in this setting.	
MRI-targeted biopsy prostate	7		O
MRI pelvis without IV contrast	6		O
CT abdomen and pelvis with IV contrast	3		☢☢☢☢
TRUS prostate	2		O
CT abdomen and pelvis without IV contrast	2		☢☢☢☢
CT abdomen and pelvis without and with IV contrast	2		☢☢☢☢
Tc-99m bone scan whole body	1		☢☢☢
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			*Relative Radiation Level

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 2: Clinically suspected prostate cancer, prior negative TRUS-guided biopsy. Detection.

Radiologic Procedure	Rating	Comments	RRL*
MRI pelvis without and with IV contrast	8		O
MRI-targeted biopsy prostate	8		O
TRUS-guided biopsy prostate	7	Repeat TRUS-guided systematic biopsy is a reasonable option, but MRI (with or without contrast) should be performed first so that MRI-targeted biopsies (fusion or in-bore technique) can be obtained from appropriate suspicious lesions.	O
MRI pelvis without IV contrast	6		O
TRUS prostate	2		O
CT abdomen and pelvis with IV contrast	2		☢☢☢☢
CT abdomen and pelvis without IV contrast	2		☢☢☢☢
CT abdomen and pelvis without and with IV contrast	2		☢☢☢☢
Tc-99m bone scan whole body	1		☢☢☢
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			*Relative Radiation Level

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 3: Clinically established low-risk prostate cancer. Active surveillance.

Radiologic Procedure	Rating	Comments	RRL*
MRI pelvis without and with IV contrast	8		O
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually			*Relative

IV contrast

Radiologic Procedure	Rating	Comments	RRL*
MRI-targeted biopsy prostate	8		O
TRUS-guided biopsy prostate	7	Serial repeat TRUS-guided systematic biopsy is standard practice for patients on active surveillance, but MRI (with or without contrast) should be performed as well so that MRI-targeted biopsies (fusion or in-bore technique) can be obtained from appropriate suspicious lesions.	O
MRI pelvis without IV contrast	7		O
TRUS prostate	2		O
CT abdomen and pelvis with IV contrast	2		☢☢☢☢
CT abdomen and pelvis without IV contrast	2		☢☢☢☢
CT abdomen and pelvis without and with IV contrast	2		☢☢☢☢
Tc-99m bone scan whole body	1		☢☢☢
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			*Relative Radiation Level

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 4: Clinically established intermediate-risk prostate cancer. Staging and/or surveillance.

Radiologic Procedure	Rating	Comments	RRL*
MRI pelvis without and with IV contrast	8		O
MRI pelvis without IV contrast	7		O
MRI-targeted biopsy prostate	6		O
CT abdomen and pelvis with IV contrast	6		☢☢☢☢
Tc-99m bone scan whole body	6		☢☢☢
TRUS-guided biopsy prostate	5		O
CT abdomen and pelvis without IV contrast	5		☢☢☢☢
TRUS prostate	2		O
CT abdomen and pelvis without and with IV contrast	2		☢☢☢☢
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			*Relative Radiation Level

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 5: Clinically established high-risk prostate cancer. Staging.

Radiologic Procedure	Rating	Comments	RRL*
MRI pelvis with and without IV contrast	8		O
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually			*Relative

Radiologic Procedure	Rating	Comments	RRL*
IV contrast			
Tc-99m bone scan whole body	8	This procedure is complementary to MRI or CT for evaluation of possible bone metastases.	☢☢☢
CT abdomen and pelvis with IV contrast	8		☢☢☢☢
CT abdomen and pelvis without IV contrast	7		☢☢☢☢
MRI pelvis without IV contrast	6		O
MRI-targeted biopsy prostate	3		O
CT abdomen and pelvis without and with IV contrast	3		☢☢☢☢
TRUS prostate	2		O
TRUS-guided biopsy prostate	2		O
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			*Relative Radiation Level

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Summary of Literature Review

Introduction/Background

Despite the frequent statement that "most men die with prostate cancer, not of it," the reality is that prostate cancer is second only to lung cancer as a cause of death from malignancy in American men. Specifically, in 2015, an estimated 220,800 American men were diagnosed with prostate cancer and 27,540 died of the disease. In addition to the personal toll of these deaths, the direct economic cost of prostate cancer in the Unites States has been estimated at approximately $10 billion per year. As with other malignancies, the primary goal during baseline evaluation of prostate cancer is disease characterization; that is, establishing disease extent, both local and distant, and aggressiveness. Determination of tumor aggressiveness is ultimately the most important factor, since this drives patient outcome.

Several special circumstances make the accurate baseline evaluation of prostate cancer particularly challenging:

> The currently available standard clinical tools used to evaluate prostate cancer, such as digital rectal examination, serum prostate-specific antigen (PSA) assay, and systematic biopsy results such as fraction of cores positive for cancer and Gleason score, are all subject to varying degrees of inaccuracy. Even radical prostatectomy, often regarded as the gold standard for pathological findings, is subject to variable interpretation. The published interobserver kappa values of 0.33 to 0.63 for the detection of extracapsular extension by different pathologists analyzing radical prostatectomy specimens are about the same as the kappa values of 0.59 to 0.67 for different radiologists looking for extracapsular extension at magnetic resonance imaging (MRI). Multiple nomograms have been described, such as the Partin Tables or the D'Amico risk stratification scheme, that aggregate data from these parameters in an attempt to better estimate tumor stage or tumor aggressiveness. These nomograms are a reasonable attempt to synthesize the data but ultimately are undermined by the inherent flaws and imprecisions of the input parameters. That said, both the D'Amico and the National Comprehensive Cancer Network (NCCN) risk stratification systems are widely used and are shown in Appendices 1 and 2 in the original guideline document. It should be noted that the number of positive biopsy cores and the clinical stage are both factors that appear to have relatively little prognostic impact when compared with the other more impactful parameters of Gleason score and PSA.

Numerous novel biomarkers have been and continue to be investigated to try and improve characterization at a patient or tumor-specific level, such as PCA3, tissue-gene signatures, serum-based microRNA, cell-free DNA, and circulating tumor cell analysis, but none has entered mainstream practice.

> Prostate cancer is a heterogeneous disease, ranging from small low-grade tumors that are indolent and incidental to large, aggressive, life-threatening tumors. This generates a twofold challenge. First, since clinicians have limited ability to precisely characterize the disease in a given patient, it is difficult to match patients to optimal treatment. Ideally, those with indolent disease would be managed by active surveillance, whereas those with higher-risk disease would receive definitive management with radiation or surgery, possibly supplemented by short- or long-term androgen deprivation therapy. Those with systemic disease require systemic treatment, typically androgen deprivation therapy followed by chemotherapy after emergence of androgen resistance. Second, the biological heterogeneity results in a protracted natural history, so outcome studies may require 10 or 15 years of follow-up to generate meaningful data. For example, after 7 years of follow-up, analysis of the European Randomized Study of Screening for Prostate Cancer showed that 1410 patients had to be screened and 48 patients had to be treated in order to save 1 life. With 6 additional years of follow-up, these numbers dropped to 781 and 27, respectively.
> Prostate cancer is a difficult organ and disease to image. For many years, the only imaging received by most patients was a transrectal ultrasound (TRUS) used to localize the prostate (*not* the cancer) prior to 6- to 12-core systematic biopsy. The emergence of multiparametric MRI over the last few decades as a powerful and relatively accurate tool for the local evaluation of prostate cancer has both enhanced and complicated the baseline evaluation of prostate cancer because it has added the option of MRI-targeted biopsy as a supplement or replacement for standard systematic biopsy, at least in the approximately 60% of patients who have an actionable target at MRI. A recent meta-analysis demonstrated that MRI-targeted biopsy significantly increases the detection rate for both all cancers and clinically significant cancers and significantly decreases the detection of clinically insignificant cancers.

Overview of Imaging Methods

The common modalities used to evaluate prostate cancer are TRUS, MRI, computed tomography (CT), and bone scintigraphy. TRUS or MRI may be combined with biopsy. TRUS and MRI are used to evaluate local disease extent, whereas CT and bone scintigraphy are used to evaluate metastatic disease, which typically involves either nodal or bone deposits. Prostate risk stratification is central in determining the appropriateness of evaluating for locally advanced or distant disease, since both are primarily detectable in intermediate- and high-risk disease alone (see Appendix 3 in the original guideline document). Although several organizations have proposed guidelines on imaging prostate cancer based on slightly differing definitions of higher-risk disease, it should be noted that the NCCN criteria for high-risk disease are any of the following:

> PSA ≥20 ng/mL
> Gleason score ≥8
> Clinical stage ≥T3
> Any 2 of: clinical stage T2b or T2c, Gleason score ≥7, PSA of 10 to 20 ng/mL

Transrectal Ultrasound

In North America, TRUS is generally performed by urologists for purposes of localizing the prostate gland (not the cancer) prior to systematic biopsy. Conventional grayscale TRUS is not widely used for tumor localization because only 11% to 35% of tumors are sonographically visible and only 17% to 57% of sonographically detected hypoechoic lesions are malignant. In a study of 31,296 cores obtained from 3912 consecutive patients undergoing TRUS with biopsy, there was no statistically significant association between the presence of a hypoechoic lesion and the detection of cancer, whether on a per-patient or per-core basis. Advanced ultrasound (US) techniques, such as Doppler, 3-dimensional (3-D) US, microbubble contrast-enhanced US, and elastography, have the potential to improve TRUS performance in the future, but none of these refinements have entered routine practice.

Transrectal Ultrasound with Biopsy

TRUS-guided systematic biopsy has been the standard diagnostic test for prostate cancer since a landmark study in 1989 showed that it was superior to digitally directed biopsy sampling of the prostate. However, because needle positioning relative to tumor location is essentially random, TRUS biopsy has a false-negative rate of 15% to 46% and a tumor undergrading rate of up to 38% when compared to final Gleason score at radical prostatectomy. So-called tumor progression based on Gleason upgrading on repeat systematic biopsy during active surveillance may simply reflect inadequate initial sampling. Despite this substantial sampling error, multiple risk stratification and management schemes rely heavily on systematic biopsy findings of Gleason grade and percentage of tumor-containing cores. Scientifically, it is suboptimal practice for such critical decision making to depend on inherently flawed data.

Multiparametric MRI

Over the last few decades, multiparametric MRI of the prostate has emerged as a powerful tool for the local evaluation of prostate cancer, including volumetric tumor localization within the prostate and assessment of local tumor extent and aggressiveness, as reviewed in more detail below according to clinical scenario. Pioneering studies in the 1980s established that cancer generally appears as an ovoid mass-like or crescentic subcapsular region of reduced T2 signal. Subsequent multicenter trials were disappointing but did not incorporate multiparametric MRI with diffusion, perfusion, or spectroscopic sequences. In particular, diffusion imaging has been seen as a "game changer" by seasoned investigators, and more recent studies using a multiparametric approach have shown substantially improved results. A recent meta-analysis incorporating 75 studies and 9796 patients showed sensitivity and specificity of 0.57 (95% confidence interval [CI], 0.49–0.64) and 0.91 (95% CI, 0.88–0.93), respectively, for the diagnosis of extracapsular extension and sensitivity and specificity of 0.58 (95% CI, 0.47–0.68) and 0.96 (95% CI, 0.95–0.97), respectively, for the diagnosis of seminal vesicle invasion. The authors concluded that MRI has high specificity but poor and heterogeneous sensitivity for local prostate cancer staging, although it should be noted that any such meta-analysis inevitably includes studies that may not be considered optimal by current state-of-the-art technical and interpretative standards. Finally, the role of intravenous gadolinium-containing contrast media merits particular attention because, although it is widely recognized that diffusion imaging is a critical component of multiparametric prostate MRI, the role of perfusion imaging is more controversial. Prostate cancer typically enhances more rapidly and washes out more quickly than benign prostatic tissue, and so detection may be aided by dynamic contrast-enhanced MRI sequences. Conversely, perfusion imaging adds time to study acquisition, poses the small risk of contrast reactions, and adds to the duration and complexity of interpretation by the radiologist tasked with reading the study. Recent work suggests the incremental benefit of perfusion imaging on tumor detection is relatively modest. Accordingly, when performing a multiparametric prostate MRI, the administration of intravenous gadolinium will likely confer only slightly improved tumor evaluation over the same study performed without contrast.

MRI-Targeted Biopsy

MRI-targeted biopsy of the prostate, after a diagnostic multiparametric MRI has depicted a focus of possible or probable malignancy, is currently a topic of major scientific interest and promises to dramatically alter the current approach to prostate cancer diagnosis. MRI-guided biopsy may be used for baseline diagnosis in patients who are biopsy naïve, for diagnosis of cancer (often in the central gland) in patients who have had a negative TRUS-guided systematic biopsy but who continue to have an elevated PSA or other cause for clinical concern, for reevaluation of tumor grade in patients on active surveillance, and for diagnosis of local recurrence in patients who have undergone prior therapy. After identification of a "high-value target," MRI-targeted biopsy can be performed in 1 of 3 ways:

Direct or "in bore": The patient is in the MRI scanner and the needle is placed in the target under MRI visualization. Generally, only the target(s) is/are sampled.
Fusion: The patient undergoes a standard TRUS-guided biopsy, but MRI targets from a preceding MRI scan are digitally "fused" to the US images so that additional cores can also be taken from those locations under US visualization.

Cognitive: The patient undergoes a standard TRUS-guided biopsy, but in addition the operator biopsies the MRI target based on visual anatomic coregistration. As might be expected, several studies, including a prospective comparative trial, have confirmed the inferiority of this approach.

Overall, the clinical paradigm for prostate cancer diagnosis is rapidly moving towards MRI-targeted transrectal biopsy, based on substantial evidence from several centers (notably the National Institutes of Health; New York University [NYU]; University of California, Los Angeles [UCLA]; and Nijmegen) that this approach can transform baseline cancer evaluation when compared with traditional systematic biopsy, with fewer false negatives, better tumor characterization, improved tumor localization, and better treatment stratification, especially stratification to lower-risk cohorts that may be appropriate for active surveillance or focal therapy.

Computed Tomography

Although the primary tumor site may be seen as a focal area of mass-like enhancement in the peripheral prostate on portal venous phase contrast-enhanced CT, the primary role of CT in prostate cancer is the detection of nodal metastases. In a meta-analysis of 24 published studies, the pooled sensitivity of CT was 0.42 (95% CI, 0.26–0.56) and pooled specificity was 0.82 (95% CI, 0.8–0.83). These relatively disappointing results likely reflect the limitations of the underlying assumption that nodal size reflects nodal content—it is well known that this paradigm has limited validity. The poor performance of CT for detection of nodal metastases has been confirmed in other recent studies. NCCN guidelines recommend CT if clinical stage is T3 or T4 or nomogram probability of lymph node involvement exceeds 10%. Recent European guidelines note that patients with stage T2 or less, PSA <10 ng/mL, Gleason score ≤6, and <50% positive biopsy cores have a <10% likelihood of having node metastases and do not need nodal evaluation.

Bone Scan

Bone scintigraphy remains the standard test used for detection of bone metastases in high-risk patients, although emerging techniques like positron emission tomography/CT with new tracers such as sodium fluoride or choline and whole-body MRI may replace the traditional bone scan in the years to come. In the absence of these advanced techniques, it is ideal if bone scintigraphy is performed at sites with single-photon emission CT/CT capability. That said, bone scintigraphy remains widely available, relatively cheap, and accurate. A recent meta-analysis demonstrated a sensitivity of 0.79 (95% CI, 0.73–0.83), a specificity of 0.82 (95% CI, 0.78–0.85), and an area under the curve of 0.89 for the diagnosis of bone metastases by bone scintigraphy. NCCN guidelines recommend bone scintigraphy if baseline PSA is ≥20, clinical stage is T2 and PSA is ≥10, clinical stage is T3 or T4, Gleason score is ≥8, or any symptoms are suggestive of bone metastases.

Discussion of Imaging Modalities by Variant

Variant 1: Clinically Suspected Prostate Cancer, No Prior Biopsy (Biopsy Naïve). Detection

Transrectal Ultrasound

In isolation, TRUS is inaccurate for prostate cancer detection and is not recommended for this purpose.

Transrectal Ultrasound–Guided Biopsy

Despite significant concerns related to both underdiagnosis and overdiagnosis, TRUS-guided systematic prostate biopsy remains the standard of care for diagnosis in patients with clinically suspected prostate cancer.

Magnetic Resonance Imaging

Historically, given the primacy of TRUS-guided systematic biopsy for prostate cancer diagnosis, MRI has not been widely used in biopsy-naïve patients with clinically suspected prostate cancer based on an abnormal digital rectal examination or serum PSA level. However, the emerging literature on the use of MRI targeting to guide baseline prostate biopsy (whether by fusion or in-bore approaches) provides strong

evidence in favor of MRI to assist in tumor localization in this population. For example, in a prospective study of 223 biopsy-naïve patients, high-value targets (i.e., lesions with a Prostate Imaging Reporting and Data System [PI-RADS] score of 4 or 5) were seen in 109 patients (49%), and 94 of these patients (86%) had positive targeted in-bore biopsies. Of the 94 patients with MRI-guided biopsies, the targeted cores showed intermediate- or high-risk disease in 90 (96%), and 16 of the patients (17%) had negative systematic biopsy results. Such results suggest prebiopsy MRI is a useful adjunct for tumor localization in biopsy-naïve patients.

MRI-Targeted Biopsy

Given the emerging data on the utility of prebiopsy diagnostic MRI for tumor localization, MRI-targeted biopsy is among the appropriate options for biopsy-naïve patients.

Computed Tomography

CT is generally not recommended unless higher-risk disease has been established histologically.

Bone Scan

Bone scintigraphy is generally not recommended unless or until the presence of higher-risk disease has been established histologically.

Variant 2: Clinically Suspected Prostate Cancer, Prior Negative TRUS-guided Biopsy. Detection

Transrectal Ultrasound

In isolation, TRUS is inaccurate for prostate cancer detection and is not recommended for this purpose.

Transrectal Ultrasound–Guided Biopsy

In patients with clinically suspected prostate cancer who have had 1 negative standard TRUS-guided systematic biopsy, a second TRUS-guided systematic biopsy will be positive in approximately 15% to 20% of cases, and so a second repeat biopsy in this setting is reasonable. The yield from additional systematic biopsies, particularly the yield of clinically significant cancer, falls off rapidly, with reported positive rates for the third biopsy of 8% to 17% and for the fourth biopsy of 7% to 12%, suggesting alternative approaches such as MRI-guided biopsy or saturation biopsy may be more appropriate in the niche setting of patients with 2 or more negative TRUS-guided systematic biopsies and persistent clinical concern for prostate cancer.

Magnetic Resonance Imaging

Emerging data suggest using MRI to localize high-value targets for possible MRI-guided biopsy is an appropriate approach to patients with clinically suspected prostate cancer and 1 or more prior negative TRUS-guided systematic biopsies. In a series of 105 patients from UCLA with a negative TRUS biopsy and persistently elevated PSA, multiparametric MRI demonstrated intermediate- and high-value targets in 34 (32%) and 14 (13%) patients, respectively, with corresponding fusion cancer detection rates of 23% and 88%. In a similar series of 172 patients from NYU, targets with suspicion scores of 3, 4, and 5 were seen in 60 (35%), 40 (23%), and 18 (10%), with overall cancer detection rates of 17%, 42%, and 89%, respectively. In a Nijmegen study of 438 patients with a PSA over 4.0 ng/mL and 1 or more prior negative TRUS biopsies, 265 patients were found to have targets worthy of MRI-guided biopsy, with a cancer detection rate of 41%. Such results suggest prebiopsy MRI is a useful adjunct for tumor localization in biopsy-negative patients.

MRI-Targeted Biopsy

Given the emerging data on the utility of prebiopsy/rebiopsy diagnostic MRI for tumor localization, MRI-targeted biopsy is among the appropriate options for biopsy-negative patients.

Computed Tomography

CT is generally not recommended unless higher-risk disease has been established histologically.

Bone Scan

Bone scintigraphy is generally not recommended unless or until the presence of higher-risk disease has been established histologically.

Variant 3: Clinically Established Low-risk Prostate Cancer. Active Surveillance

Transrectal Ultrasound

TRUS is inaccurate for prostate cancer detection and also has limited accuracy for prostate cancer staging and so is not generally recommended for the evaluation of patients on active surveillance.

Transrectal Ultrasound–Guided Biopsy

Many active surveillance programs incorporate serial PSA testing and annual repeat TRUS biopsies, and some form of serial biopsy regimen is certainly the standard practice, although compliance with recommendations for serial biopsy is low.

Magnetic Resonance Imaging

The role of MRI in active surveillance has recently been the subject of a meta-analysis incorporating 7 studies and 1028 patients. MRI demonstrated an unrecognized significant lesion in 33% of patients, and targeted biopsy demonstrated disease unsuitable for continued active surveillance in 15% of these cases. Conversely, only 6% of patients with a negative MRI were found to be outside criteria for active surveillance on repeat biopsy. In another study of 111 patients on active surveillance, multiparametric MRI showed actionable targets (PI-RADS scores of 3, 4, or 5) in 70 patients (63%). Sixty-nine of these 70 patients proceeded to targeted biopsy, which was positive in 31, including 16 patients with Gleason pattern 4 or above that was considered to preclude continuation on active surveillance. A study from Toronto showed high-value targets (Likert scores of 4 or 5) in 37 of 71 (52%) patients on active surveillance. Fusion-targeted biopsy was positive for Gleason 7+ cancer in 18 of these 37 patients, including 16 in whom the higher-grade cancer was present specifically in the targeted cores. Conversely, only 1 of the 35 patients without a high-value target was found to have Gleason 7+ cancer on rebiopsy. Other similar studies have confirmed that a negative MRI is a favorable prognostic finding in patients on active surveillance, and only 9% of such patients are reclassified to higher-risk disease on repeat biopsy.

MRI-Targeted Biopsy

Existing data support the use of MRI to look for visible disease as a potential biopsy target in men on active surveillance. The use of serial MRI to evaluate disease progression is intuitively appealing, but as noted in a recent systematic review, "Robust data on the use of repeat MRI in active surveillance are lacking. Prospective studies with clear definitions of radiological significance and progression are needed before this approach can be adopted."

Computed Tomography

CT is generally not recommended unless higher-risk disease has been established.

Bone Scan

Bone scintigraphy is generally not recommended unless higher-risk disease has been established.

Variant 4: Clinically Established Intermediate-Risk Prostate Cancer. Staging and/or Surveillance

Transrectal Ultrasound

TRUS is unlikely to provide useful incremental information in patients with an established diagnosis of intermediate-risk prostate cancer and so is not recommended.

Transrectal Ultrasound–Guided Biopsy

Some publications have suggested that active surveillance may be an appropriate management option for

at least a subset of patients with intermediate-risk prostate cancer. In that setting, some form of serial TRUS-guided biopsy would be appropriate as part of the monitoring regimen.

Magnetic Resonance Imaging

In addition to standard local and nodal staging observations, multiparametric MRI may be helpful in the management of intermediate-risk prostate cancer by revealing unfavorable disease in patients who may be considering active surveillance, demonstrating more extensive disease that may merit supplementary extended androgen deprivation therapy, localizing dominant disease for focal therapy, or guiding surgical planning.

MRI-Targeted Biopsy

Many patients with intermediate-risk disease choose definitive therapy, and targeted biopsy is unlikely to significantly alter management or prognostic counseling. However, MRI-targeted biopsy in patients with established intermediate-risk disease may be appropriate in selected circumstances, for example, in patients with Gleason score 3+4 cancer who might be considering active surveillance but who would opt for more aggressive therapy if targeted biopsy demonstrated Gleason score 4+3 or higher disease.

Computed Tomography

CT or MRI for nodal staging is generally appropriate in intermediate-risk patients, since the a priori risk of nodal disease exceeds 10%.

Bone Scan

NCCN guidelines and existing literature recommend bone scintigraphy if baseline PSA is ≥20, clinical stage is T2 and PSA is ≥10, clinical stage is T3 or T4, Gleason score is ≥8, or any symptoms are suggestive of bone metastases. Many intermediate-risk patients would meet these criteria.

Variant 5: Clinically Established High-Risk Prostate Cancer. Staging

Transrectal Ultrasound

TRUS is unlikely to provide useful incremental information in patients with an established diagnosis of high-risk prostate cancer and so is not recommended.

Transrectal Ultrasound–Guided Biopsy

TRUS-guided biopsy is unlikely to provide useful incremental information in patients with an established diagnosis of high-risk prostate cancer and so is not recommended.

Magnetic Resonance Imaging

In addition to standard local and nodal staging observations, multiparametric MRI may be helpful in the management of high-risk prostate cancer by demonstrating more extensive disease that may merit supplementary extended androgen deprivation therapy, localizing dominant disease for focal therapy, or guiding surgical planning.

MRI-Targeted Biopsy

Most patients with high-risk disease require definitive therapy, and targeted biopsy is unlikely to significantly alter management or prognostic counseling.

Computed Tomography

CT or MRI for nodal staging is generally appropriate in high-risk patients, since the a priori risk of nodal disease exceeds 10%.

Bone Scan

NCCN guidelines and existing literature recommend bone scintigraphy if baseline PSA is ≥20, clinical

stage is T2 and PSA is ≥10, clinical stage is T3 or T4, Gleason score is ≥8, or any symptoms are suggestive of bone metastases. Essentially all high-risk patients would meet these criteria.

Summary of Recommendations

For diagnosis of prostate cancer, TRUS-guided systematic biopsy remains the standard procedure in routine clinical practice. However, MRI-targeted biopsy of high-value lesions identified at multiparametric MRI, whether by fusion or in-bore techniques, is increasingly emerging as an important diagnostic tool that may be used to supplement (and perhaps someday supplant) TRUS-guided biopsy. MRI-targeted biopsy necessarily requires performance of a preceding multiparametric MRI. MRI-targeted biopsy is particularly appropriate for patients with an elevated PSA after 1 or more negative TRUS-guided biopsies who have a high-value target at diagnostic multiparametric MRI.
For monitoring of lower-risk prostate cancer being managed by active surveillance, serial TRUS-guided systematic biopsy remains a standard component of active surveillance regimens. MRI-targeted biopsy of high-value lesions identified at multiparametric MRI, whether by fusion or in-bore techniques, is increasingly emerging as an important supplementary tool that often results in tumor upgrading. The role of serial multiparametric MRI as part of a surveillance regimen is undetermined.
For staging of intermediate- or higher-risk prostate cancer, multiparametric MRI offers reasonable accuracy in the evaluation of extracapsular extension and seminal vesicle invasion. MRI or CT can be used to evaluate pelvic and retroperitoneal lymph nodes, whereas bone scintigraphy remains the standard procedure for evaluation of possible bone metastases.

Abbreviations

CT, computed tomography
IV, intravenous
MRI, magnetic resonance imaging
Tc-99m, technetium-99 metastable
TRUS, transrectal ultrasound

Relative Radiation Level Designations

Relative Radiation Level*	Adult Effective Dose Estimate Range	Pediatric Effective Dose Estimate Range
O	0 mSv	0 mSv
☢	<0.1 mSv	<0.03 mSv
☢☢	0.1-1 mSv	0.03-0.3 mSv
☢☢☢	1-10 mSv	0.3-3 mSv
☢☢☢☢	10-30 mSv	3-10 mSv
☢☢☢☢☢	30-100 mSv	10-30 mSv
*RRL assignments for some of the examinations cannot be made, because the actual patient doses in these procedures vary as a function of a number of factors (e.g., region of the body exposed to ionizing radiation, the imaging guidance that is used). The RRLs for these examinations are designated as "Varies."		

Clinical Algorithm(s)

Algorithms were not developed from criteria guidelines.

Scope

Disease/Condition(s)

Prostate cancer

Guideline Category

Diagnosis

Evaluation

Risk Assessment

Clinical Specialty

Internal Medicine

Nuclear Medicine

Oncology

Radiology

Urology

Intended Users

Advanced Practice Nurses

Health Plans

Hospitals

Managed Care Organizations

Physician Assistants

Physicians

Students

Utilization Management

Guideline Objective(s)

To evaluate the appropriateness of imaging procedures for pretreatment detection, surveillance, and staging of patients with prostate cancer

Target Population

Patients with suspected or confirmed prostate cancer

Interventions and Practices Considered

1. Biopsy, prostate
    - Transrectal ultrasound (TRUS)-guided
    - Magnetic resonance imaging (MRI)-targeted
2. MRI, pelvis
    - Without and with intravenous (IV) contrast

    - Without IV contrast
3. Computed tomography (CT), abdomen and pelvis
    - With IV contrast
    - Without IV contrast
    - Without and with IV contrast
4. TRUS, prostate
5. Technetium (Tc)-99m bone scan, whole body

Major Outcomes Considered

- Utility of imaging procedures in detection, surveillance, and staging of prostate cancer
- Accuracy, sensitivity, specificity, and positive and negative predictive value of imaging procedures for detection, surveillance, and staging of prostate cancer

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Literature Search Summary

Of the 118 citations in the original bibliography, 17 were retained in the final document.

A literature search was conducted in April 2015 and July 2016 to identify additional evidence published since the *ACR Appropriateness Criteria® Prostate Cancer–Pretreatment Detection, Surveillance, and Staging* topic was finalized. Using the search strategies described in the literature search companion (see the "Availability of Companion Documents" field), 2503 articles were found. Sixty-four articles were added to the bibliography. One hundred fifty-two articles were not used as they were duplicates already cited in the original bibliography or captured in more than one literature search. The remaining articles were not used due to either poor study design, the articles were not relevant or generalizable to the topic, or the results were unclear or biased.

The author added 12 citations from bibliographies, Web sites, or books that were not found in the literature searches.

See also the American College of Radiology (ACR) Appropriateness Criteria® literature search process document (see the "Availability of Companion Documents" field) for further information.

Number of Source Documents

Of the 118 citations in the original bibliography, 17 were retained in the final document. The literature search conducted in April 2015 and July 2016 identified 64 articles that were added to the bibliography. The author added 12 citations from bibliographies, Web sites, or books that were not found in the literature searches.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Definitions of Study Quality Categories

Category 1 - The study is well-designed and accounts for common biases.

Category 2 - The study is moderately well-designed and accounts for most common biases.

Category 3 - The study has important study design limitations.

Category 4 - The study or source is not useful as primary evidence. The article may not be a clinical study, the study design is invalid, or conclusions are based on expert consensus.

> The study does not meet the criteria for or is not a hypothesis-based clinical study (e.g., a book chapter or case report or case series description);
>
> *Or*
>
> The study may synthesize and draw conclusions about several studies such as a literature review article or book chapter but is not primary evidence;
>
> *Or*
>
> The study is an expert opinion or consensus document.

Category M - Meta-analysis studies are not rated for study quality using the study element method because the method is designed to evaluate individual studies only. An "M" for the study quality will indicate that the study quality has not been evaluated for the meta-analysis study.

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

The topic author assesses the literature then drafts or revises the narrative summarizing the evidence found in the literature. American College of Radiology (ACR) staff drafts an evidence table based on the analysis of the selected literature. These tables rate the study quality for each article included in the narrative.

The expert panel reviews the narrative, evidence table and the supporting literature for each of the topic-variant combinations and assigns an appropriateness rating for each procedure listed in the variant table(s). Each individual panel member assigns a rating based on his/her interpretation of the available evidence.

More information about the evidence table development process can be found in the ACR Appropriateness Criteria® Evidence Table Development document (see the "Availability of Companion Documents" field).

Methods Used to Formulate the Recommendations

Expert Consensus (Delphi)

Description of Methods Used to Formulate the Recommendations

Rating Appropriateness

The American College of Radiology (ACR) Appropriateness Criteria (AC) methodology is based on the RAND Appropriateness Method. The appropriateness ratings for each of the procedures or treatments included in the AC topics are determined using a modified Delphi method. A series of surveys are conducted to elicit each panelist's expert interpretation of the evidence, based on the available data, regarding the appropriateness of an imaging or therapeutic procedure for a specific clinical scenario. The expert panel members review the evidence presented and assess the risks or harms of doing the procedure balanced with the benefits of performing the procedure. The direct or indirect costs of a procedure are not considered as a risk or harm when determining appropriateness. When the evidence for a specific topic and variant is uncertain or incomplete, expert opinion may supplement the available evidence or may be the sole source for assessing the appropriateness.

The appropriateness is represented on an ordinal scale that uses integers from 1 to 9 grouped into three categories: 1, 2, or 3 are in the category "usually not appropriate" where the harms of doing the procedure outweigh the benefits; and 7, 8, or 9 are in the category "usually appropriate" where the benefits of doing a procedure outweigh the harms or risks. The middle category, designated "may be appropriate," is represented by 4, 5, or 6 on the scale. The middle category is when the risks and benefits are equivocal or unclear, the dispersion of the individual ratings from the group median rating is too large (i.e., disagreement), the evidence is contradictory or unclear, or there are special circumstances or subpopulations which could influence the risks or benefits that are embedded in the variant.

The ratings assigned by each panel member are presented in a table displaying the frequency distribution of the ratings without identifying which members provided any particular rating. To determine the panel's recommendation, the rating category that contains the median group rating without disagreement is selected. This may be determined after either the first or second rating round. If there is disagreement after the second rating round, the recommendation is "May be appropriate."

This modified Delphi method enables each panelist to articulate his or her individual interpretations of the evidence or expert opinion without excessive influence from fellow panelists in a simple, standardized, and economical process. For additional information on the ratings process see the Rating Round Information document.

Additional methodology documents, including a more detailed explanation of the complete topic development process and all ACR AC topics can be found on the ACR Web site (see also the "Availability of Companion Documents" field).

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

Criteria developed by the Expert Panels are reviewed by the American College of Radiology (ACR)

Committee on Appropriateness Criteria.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The recommendations are based on analysis of the current medical evidence literature and the application of the RAND/UCLA appropriateness method and expert panel consensus.

Summary of Evidence

Of the 93 references cited in the *ACR Appropriateness Criteria® Prostate Cancer—Pretreatment Detection Staging and Surveillance* document, 1 reference is categorized as a good-quality therapeutic reference. Additionally, 87 references are categorized as diagnostic references including 3 well-designed studies, 23 good-quality studies, and 33 quality studies that may have design limitations. There are 28 references that may not be useful as primary evidence. There are 5 references that are meta-analysis studies.

Although there are references that report on studies with design limitations, 27 well-designed or good-quality studies provide good evidence.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Magnetic resonance imaging (MRI)-targeted transrectal biopsy can transform baseline cancer evaluation when compared with traditional systematic biopsy, with fewer false negatives, better tumor characterization, improved tumor localization, and better treatment stratification, especially stratification to lower-risk cohorts that may be appropriate for active surveillance or focal therapy.

Potential Harms

- Because needle positioning relative to tumor location is essentially random, transrectal ultrasound (TRUS) biopsy has a false-negative rate of 15% to 46% and a tumor undergrading rate of up to 38% when compared to final Gleason score at radical prostatectomy.
- Prostate cancer typically enhances more rapidly and washes out more quickly than benign prostatic tissue, and so detection may be aided by dynamic contrast-enhanced magnetic resonance imaging (MRI) sequences. Conversely, perfusion imaging adds time to study acquisition, poses the small risk of contrast reactions, and adds to the duration and complexity of interpretation by the radiologist tasked with reading the study.

Relative Radiation Level Information

Potential adverse health effects associated with radiation exposure are an important factor to consider when selecting the appropriate imaging procedure. Because there is a wide range of radiation exposures associated with different diagnostic procedures, a relative radiation level (RRL) indication has been included for each imaging examination. The RRLs are based on effective dose, which is a radiation dose quantity that is used to estimate population total radiation risk associated with an imaging procedure. Patients in the pediatric age group are at inherently higher risk from exposure, both because of organ sensitivity and longer life expectancy (relevant to the long latency that appears to accompany radiation exposure). For these reasons, the RRL dose estimate ranges for pediatric examinations are lower as

compared to those specified for adults. Additional information regarding radiation dose assessment for imaging examinations can be found in the American College of Radiology (ACR) Appropriateness Criteria® Radiation Dose Assessment Introduction document (see the "Availability of Companion Documents" field).

Qualifying Statements

Qualifying Statements

- The American College of Radiology (ACR) Committee on Appropriateness Criteria and its expert panels have developed criteria for determining appropriate imaging examinations for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide radiologists, radiation oncologists, and referring physicians in making decisions regarding radiologic imaging and treatment. Generally, the complexity and severity of a patient's clinical condition should dictate the selection of appropriate imaging procedures or treatments. Only those examinations generally used for evaluation of the patient's condition are ranked. Other imaging studies necessary to evaluate other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate imaging procedures or treatments. Imaging techniques classified as investigational by the U.S. Food and Drug Administration (FDA) have not been considered in developing these criteria; however, study of new equipment and applications should be encouraged. The ultimate decision regarding the appropriateness of any specific radiologic examination or treatment must be made by the referring physician and radiologist in light of all the circumstances presented in an individual examination.
- ACR seeks and encourages collaboration with other organizations on the development of the ACR Appropriateness Criteria through society representation on expert panels. Participation by representatives from collaborating societies on the expert panel does not necessarily imply society endorsement of the final document.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Chart Documentation/Checklists/Forms

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Coakley FV, Oto A, Alexander LF, Allen BC, Davis BJ, Froemming AT, Fulgham PF, Hosseinzadeh K, Porter C, Sahni VA, Schuster DM, Showalter TN, Venkatesan AM, Verma S, Wang CL, Remer EM, Eberhardt SC, Expert Panel on Urologic Imaging. ACR Appropriateness CriteriaÂ® prostate cancerâ€"pretreatment detection, surveillance, and staging. Reston (VA): American College of Radiology (ACR); 2016. 16 p. [93 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2016

Guideline Developer(s)

American College of Radiology - Medical Specialty Society

Source(s) of Funding

The American College of Radiology (ACR) provided the funding and the resources for these ACR Appropriateness Criteria®.

Guideline Committee

Committee on Appropriateness Criteria, Expert Panel on Urologic Imaging

Composition of Group That Authored the Guideline

Panel Members: Fergus V. Coakley, MD (*Principal Author*); Aytekin Oto, MD (*Panel Vice-chair*); Lauren F. Alexander, MD; Brian C. Allen, MD; Brian J. Davis, MD, PhD; Adam T. Froemming, MD; Pat F. Fulgham, MD; Keyanoosh Hosseinzadeh, MD; Christopher Porter, MD; V. Anik Sahni, MD; David M. Schuster, MD; Timothy N. Showalter, MD, MPH; Aradhana M. Venkatesan, MD; Sadhna Verma, MD; Carolyn L. Wang, MD; Erick M. Remer, MD (*Specialty Chair*); Steven C. Eberhardt, MD (*Panel Chair*)

Financial Disclosures/Conflicts of Interest

Not stated

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Eberhardt SC, Carter S, Casalino DD, Merrick G, Frank SJ, Gottschalk AR, Leyendecker JR, Nguyen PL, Oto A, Porter C, Remer EM, Rosenthal SA, Expert Panels on Urologic Imaging and Radiation Oncology-Prostate. ACR Appropriateness Criteria® prostate cancer -- pretreatment detection, staging, and surveillance. [online publication]. Reston (VA): American College of Radiology (ACR); 2012. 12 p. [119 references]

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the American College of Radiology (ACR) Web site .

Availability of Companion Documents

The following are available:

- ACR Appropriateness Criteria®. Overview. Reston (VA): American College of Radiology; 2015 Oct. 3 p. Available from the American College of Radiology (ACR) Web site .
- ACR Appropriateness Criteria®. Literature search process. Reston (VA): American College of Radiology; 2015 Feb. 1 p. Available from the ACR Web site .
- ACR Appropriateness Criteria®. Evidence table development. Reston (VA): American College of Radiology; 2015 Nov. 5 p. Available from the ACR Web site .
- ACR Appropriateness Criteria®. Topic development process. Reston (VA): American College of Radiology; 2015 Nov. 2 p. Available from the ACR Web site .
- ACR Appropriateness Criteria®. Rating round information. Reston (VA): American College of Radiology; 2015 Apr. 5 p. Available from the ACR Web site .
- ACR Appropriateness Criteria®. Radiation dose assessment introduction. Reston (VA): American College of Radiology; 2016. 4 p. Available from the ACR Web site .
- ACR Appropriateness Criteria®. Manual on contrast media. Reston (VA): American College of Radiology; 2016. 128 p. Available from the ACR Web site .
- ACR Appropriateness Criteria®. Procedure information. Reston (VA): American College of Radiology; 2016 May. 2 p. Available from the ACR Web site .
- ACR Appropriateness Criteria® prostate cancer—pretreatment detection, surveillance and staging. Evidence table. Reston (VA): American College of Radiology; 2016. 41 p. Available from the ACR Web site .
- ACR Appropriateness Criteria® prostate cancer—pretreatment detection, surveillance and staging. Literature search. Reston (VA): American College of Radiology; 2016. 2 p. Available from the ACR Web site .

In addition, Appendices 1 and 2 of the original guideline document provide the D'Amico and the National Comprehensive Cancer Network (NCCN) risk stratification systems, and Appendix 3 provides a table depicting the likelihood of locally advanced or distant disease in prostate cancer stratified by D'Amico.

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI on November 15, 2004. The information was verified by the

guideline developer on December 21, 2004. This summary was updated by ECRI on March 23, 2006, December 4, 2007, and on June 17, 2010. This summary was updated by ECRI Institute on January 13, 2011 following the U.S. Food and Drug Administration (FDA) advisory on gadolinium-based contrast agents. This summary was updated by ECRI Institute on May 9, 2013. This summary was updated by ECRI Institute on March 23, 2017.

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